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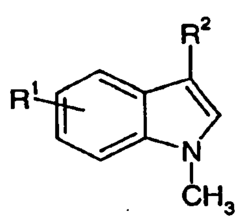
(54) Title: METHYLATION OF INDOLE COMPOUNDS USING DIMETHY CARBONATE



(I)

(57) Abstract: A process for manufacturing a methylated indole compounds of formula (I) from the non-methylated precursor with dimethyl carbonate in the presence of a base and/or catalyst at ambient pressure wherein R^1 and R^2 are defined in the description and claims.

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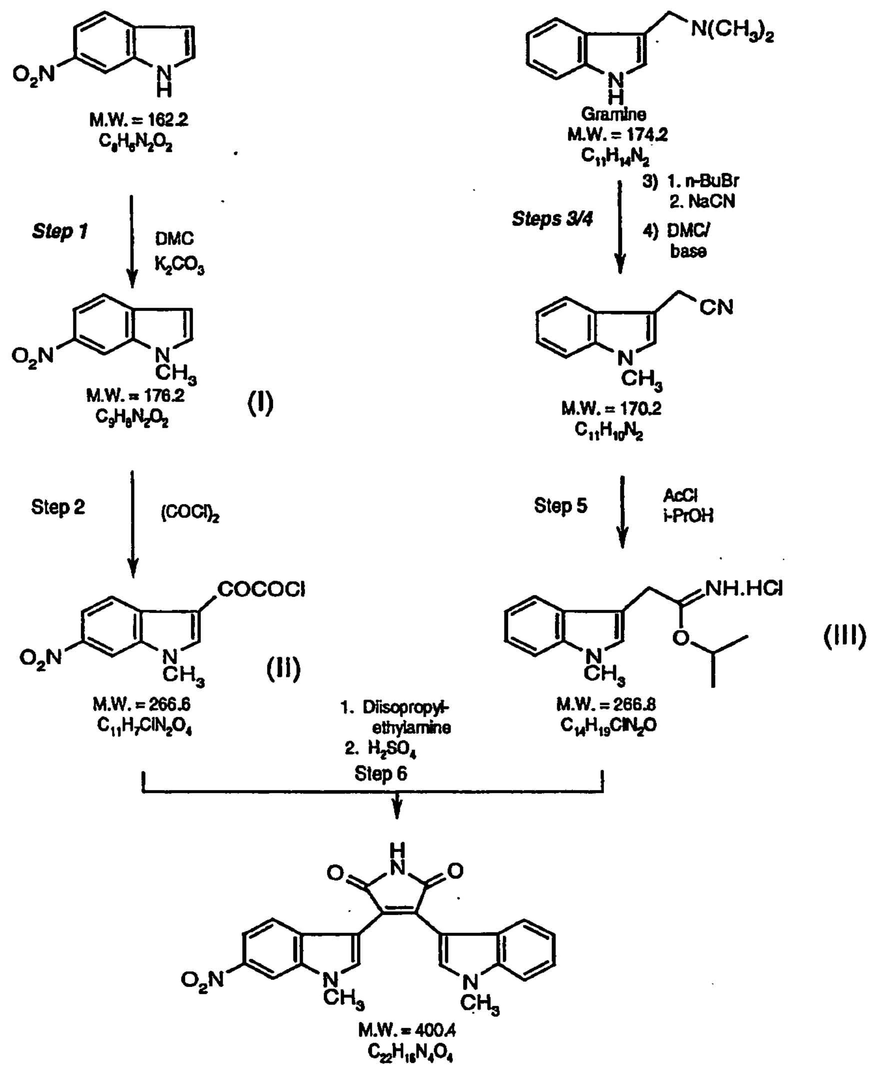
The following scheme shows a method for preparing 3-(1-methyl-3-indolyl)-4-(1-methyl-6-nitro-3-indolyl)-1H-pyrrole-2,5-dione.



Common methylating agents, such as methyl halides (MeX; X=Cl, Br, I) and dimethylsulfate ("DMS"), can be used to methylate O-, C- and N- under mild reaction conditions. However, as described above for methyl iodide, these agents pose severe concerns from environmental and process safety standpoints. On the other hand, dimethyl carbonate is a comparatively safe, non toxic and environmentally friendly methylating

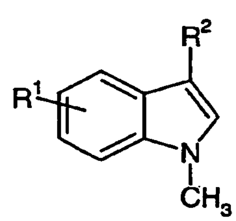
agent. The by-products of its use, methanol and carbon dioxide, are not associated with disposal problems. Moreover, for the manufacture of antimitotic agents of the above class, which require two indole ring methylations, the need is double. Although it has been reported (Tondo, P., Selva, M., and Bomben, A., *Org. Synth.* 1998, *76*, 169) that DMC can be used to methylate the alpha position of an arylacetonitrile, nowhere has it been suggested to use DMC for methylating indole ring containing compounds, much less the N-methylation of indole rings.

Unfortunately, the use of DMC in prior art processes typically requires high reaction temperatures (>180 ^{0}C), a stainless steel autoclave, high pressure, and a large excess of dimethyl carbonate (as solvent and methylating agent). With the help of catalysts, lower reaction temperatures (100 ^{0}C) can be used. However, such catalysts (e.g. crown ether) are generally very toxic and pressurized reaction chambers are required.

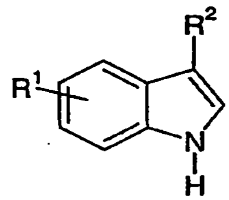
The inventive use of dimethyl carbonate for N-methylation of an indole ring forms a part of the subject invention and was disclosed in the European Patent Application EP 00/13026.

Therefore, the subject invention fulfills a need in the art for a green process for methylating the nitrogen atom in an indole compound under conditions that do not require high pressure or temperature.

The subject invention provides a process for manufacturing a methylated indole compounds of the formula I



where R^1 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, -OCH_3, -NO_2, -CHO, -CO_2CH_3, and -CN, and R^2 is selected from the group consisting of C_1-C_6 alkyl, -CO_2CH_3, -CN, -CHO, -NH_2, -N(C_1-C_6 alkyl)$_2$, -$(CH_2)_n$COOH, and -$(CH_2)_n$CN, where n is an integer from 1 to 4, inclusive. The process comprises reacting a compound of the formula :



wherein R^1 and R^2 are as above, with dimethyl carbonate in the presence of a suitable base or catalyst at ambient pressure.

In a preferred embodiment, when R^1 is nitro and at position 6, R^2 is hydrogen. In another preferred embodiment, when R^1 is hydrogen, R^2 is acetonitrile.

In the present description the term “alkyl”, alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 6 carbon atom. Examples of straight-chain and branched C_1-C_6 alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, the isomeric pentyls, and the isomeric hexyls.

The term "alkenyl" refers to a hydrocarbon chain as defined for alkyl having at least one olefinic double bond (including for example, vinyl, allyl and butenyl).

Typically, the reacting is at a temperature between about 120 °C and about 134 °C, more preferrably between about 126 °C and about 130 °C.

It is preferred that the reacting is in the presence of a solvent, such as N,N-dimethylformamide and 1-methyl-2-pyrrolidinone, the most preferred solvent being N,N-dimethylformamide.

Favorably, the reacting is in the presence of a phase transfer catalyst, such as tetrabutylammonium bromide or 18-crown-6, the most favorable catalyst being tetrabutylammonium bromide. Phase transfer catalysts are known in the art and described e.g. in Surv. Prog Chem. 9, 1-54 (1980); Chem. Unserer Zeit 12, 161-168 (1978); Makosza, in Scheffold, Modern Synthetic Methods, Bd. 1, S. 7-100, Frankfurt: Salle u. Sauerländer 1976. Polymer 20, 1048 ff. (1979). Angew. Chem. 91, 464-472 (1979).

The process can involve reacting is in the presence of a base, such as potassium hydroxide, sodium hydroxide, and potassium carbonate, the most favorable base being potassium carbonate.

The base may be an alkali metal hydroxide or an alkali metal carbonate. Of course the reacting can in the presence of both a base and a catalyst.

For example, it is favored where the base is selected from the group consisting of potassium hydroxide, sodium hydroxide, and potassium carbonate, and the catalyst is a phase transfer catalyst. Favored bases are selected from the group consisting of potassium hydroxide, sodium hydroxide, and potassium carbonate, and favored catalysts are selected from the group consisting of tetrabutylammonium bromide and 18-crown-6.

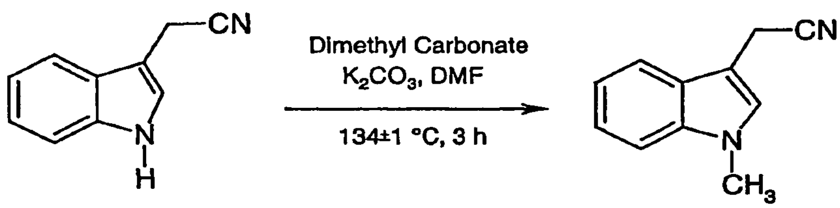
The reaction time can vary but is readily determined by the skilled artisan. Favorable reations times are between 0.75 hour and 36 hours, preferrably between 1 hour and 26 hours, and most preferrably between 1 hour and 10 hours.

EXAMPLES

The experiments in the following examples have actually been performed.

Example 1

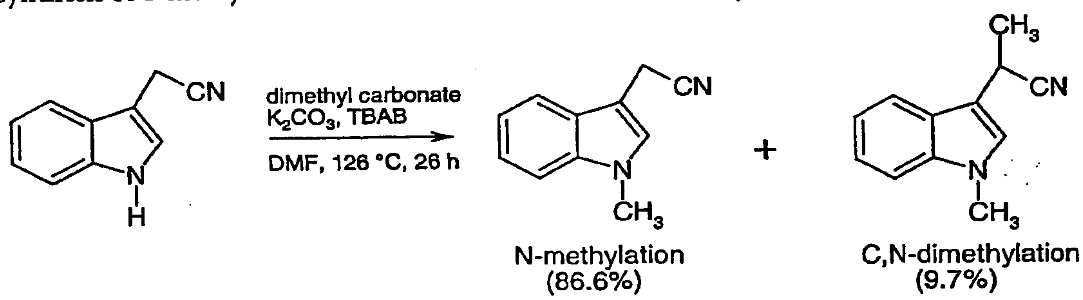
Preparation of 1-methylindole-3-acetonitrile



A 500 mL, three-necked flask equipped with a thermocouple, condenser, and addition funnel was charged with indole-3-acetonitrile (10.0g, 0.064 mol), potassium carbonate (5.0g, 36 mmol), N,N-dimethylformamide (60 mL) and dimethyl carbonate (11.0 mL, 0.13 mol). The resulting mixture was heated to 124±1°C. The progress of the reaction was monitored by HPLC. After 10 h at this temperature, the presence of the starting indole could not be detected. The reaction mixture was then cooled to zero to -5°C. Water (140mL) was added which resulted in the formation of a precipitate. The mixture was stirred at –5 °C for 1 hour, then the solid was collected by filtration, washed with water (150 mL), and dried under high vacuum at 45°C for 24 h to give 1-methylindole-3-acetonitrile (I and II, 9.69g, 89%) as a brown solid.

Example 2

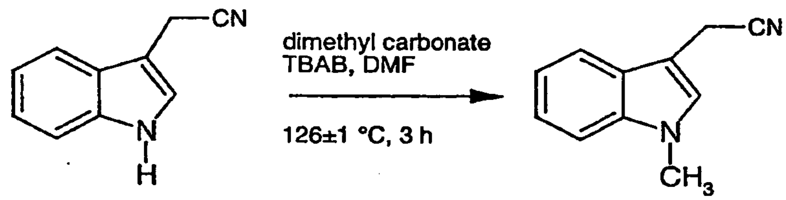
Synthesis of 1-methylindole-3-acetonitrile and rac.-2-(1-methylindol-3-yl)propionitrile.



A mixture of indole-3-acetonitrile (5.0g, 32.01 mmol), potassium carbonate (powder, 2.5g), dimethyl carbonate (10 mL, 118.8 mmol), N,N-dimethylformamide (40 mL) and tetrabutylammonium bromide 0.5g were mixed together and heated to 126 °C for 6 h. Then a second portion of dimethyl carbonate (3 mL, 35.6 mmol) was added and mixture was refluxed for another 17 h. Starting material was still present, so an third portion of dimethyl carbonate (3 mL, 35.6 mmol) was added and the reaction mixture was refluxed for another 3 h. Analysis of the reaction mixture at this point showed it to be mainly a mixture of two compounds, 1-methylindole-3-acetonitrile (86.6%) along with a second minor component identified as rac.-2-(1-methylindol-3-yl)propionitrile (9.7%). Starting indole could not be detected. The reaction mixture was cooled to room temperature, then was diluted with water (80 mL) and extracted with tert-butyl methyl ether (100 mL) The separated organic layer was washed twice with water (100 mL) then the solution was concentrated under vacuum to ~20 mL. The concentrate was cooled in an ice-bath as heptane (100 mL) was added drop-wise with vigorous stirring. The mixture was cooled to –15 °C and the resulting solid was filtered off, washed with heptane (50 mL) and dried under vacuum at 25 °C to give 1-methylindole-3-acetonitrile (I) and rac.-2-(1-methylindol-3-yl)propionitrile (II).

Example 3

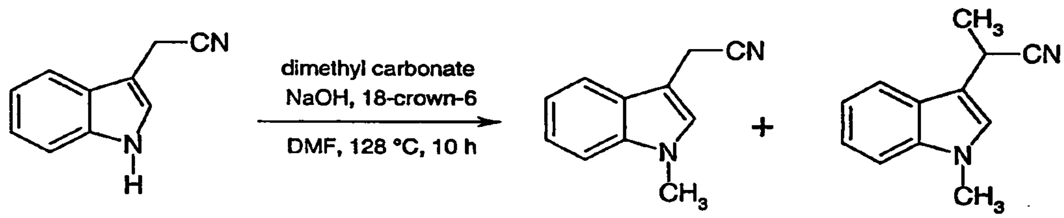
Preparation of 1-methylindole-3-acetonitrile.



A 1 L, three-necked flask equipped with a thermocouple, condenser, and addition funnel was charged with indole-3-acetonitrile (58.0g, 90% pure = 0.334 mol), tetrabutylammonium bromide (11.6g, 36 mmol), N,N-dimethylformamide (348 mL) and dimethyl carbonate (92.8 mL, 1.10 mol) and the resulting mixture was heated to 126±1°C. The progress of the reaction was monitored by HPLC and after 3 h at this temperature, the presence of remaining starting indole could not be detected. After the reaction mixture was then cooled to zero to -5°C, water (696 mL) was added which resulted in the formation of a precipitate. The mixture was stirred at –5 °C for 1 hour, then the solid was collected by filtration, washed with water (150 mL) and dried under high vacuum at 45°C for 24 h to give 1-methylindole-3-acetonitrile (52.0g, 91.5%) as a brown solid.

Example 5

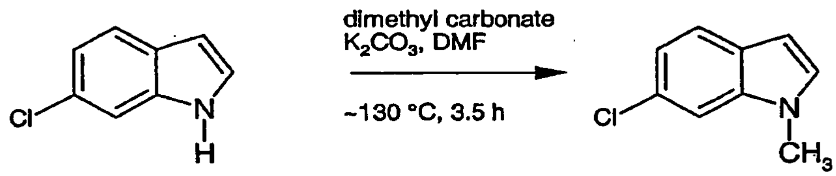
Synthesis of 1-methylindole-3-acetonitrile and rac.-2-(1-methylindol-3-yl)propionitrile.



A 250 mL, three-necked flask was charged with indole-3-acetonitrile (5.0g, 32.0 mmol), sodium hydroxide (pallet, 2.5g), dimethyl carbonate (6.6. mL, 78.3 mmol), N,N-dimethylformamide (40 mL), and 25 mg of 18-crown-6 . The resulting mixture was heated to 127 °C for 10 h. Analysis of the reaction mixture at this point showed it to be mainly a mixture of two compounds, 1-methylindole-3-acetonitrile (90.8%) along with a second minor component identified as rac.-2-(1-methylindol-3-yl)propionitrile (3.0%). No starting indole was detected. The reaction mixture was cooled to room temperature, then was diluted with water (100mL). The mixture was cooled to –15 °C , and a precipitate formed. The mixture was stirred at this temperature for 1 h. The resulting solid was filtered off, washed with heptane (50 mL), and dried under vacuum at 25 °C to give 4.3g of 1-methylindole-3-acetonitrile(I) and C,N-dimethylated by-product (II).

Example 8

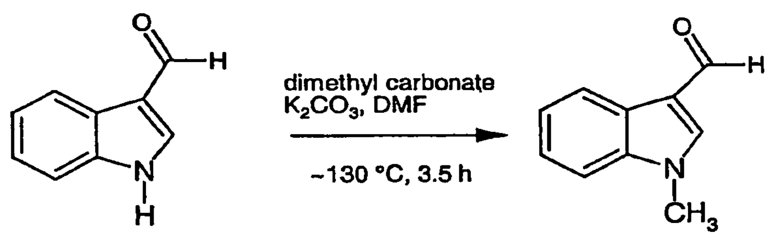
Preparation of 6-chloro-1-methylindole.



6-Chloroindole (1.0g, 6.59 mmol), potassium carbonate (0.5g), N,N-dimethylformamide (10 mL) and dimethyl carbonate (1.7 mL, 20.21 mmol) were stirred and heated to reflux (~130 °C). The starting indole was consumed within 3.5 h (as determined by HPLC). After the mixture was then cooled to ~3 °C, ice cold water (50 mL) was added and the resulting oily suspension was extracted with tert-butyl methyl ether (40 mL). The separated organic layer was washed with water (3 x 25 mL), then was evaporated under vacuum to furnish 5-chloro-1-methylindole as a light yellow oil (1.05g, 96.1% yield).

Example 9

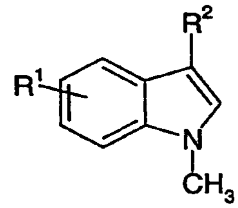
Preparation of 1-methylindole-3-carboxaldehyde.



A mixture of indole-3-carboxaldehyde (3g, 20.67 mmol), potassium carbonate (1.5g), N,N-dimethylformamide (20 mL) and dimethyl carbonate (5.2 mL, 61 mmol) were stirred and heated to reflux (~130 °C). At various time intervals, the progress of the reaction was monitored by HPLC and it was shown to be complete within 3.5 h. The reaction mixture

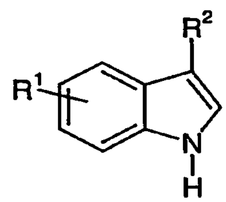
CLAIMS

1. A process for manufacturing a methylated indole compounds of the formula I



where R^1 is selected from the group consisting of halogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, $-OCH_3$, $-NO_2$, -CHO, $-CO_2CH_3$, and -CN, and R^2 is selected from the group consisting of C_1-C_6 alkyl, $-CO_2CH_3$, -CN, -CHO, $-NH_2$, $-N(C_1$-C_6 alkyl$)_2$, $-(CH_2)_nCOOH$, and $-(CH_2)_nCN$, where n is an integer from 1 to 4, inclusive,

which comprises reacting a compound of the formula :



wherein R^1 and R^2 are as above, with dimethyl carbonate in the presence of a base and/or catalyst at ambient pressure.

2. The process of claim 1, wherein the reaction is in the presence of a solvent.

3. The process of claims 1-2, wherein the reaction is in the presence of a solvent selected from the group consisting of N,N-dimethylformamide and 1-methyl-2-pyrrolidinone.

4. The process of claims 1-3, wherein the reaction is in the presence N,N-dimethylformamide.

5. The process of claims 1-4, wherein the reaction is in the presence of a phase transfer catalyst.

6. The process of claims 1-5, wherein the reaction is in the presence of a phase transfer catalyst selected from the group consisting of tetrabutylammonium bromide or 18-crown-6.

7. The process of claims 1-6, wherein the phase transfer catalyst is tetrabutylammonium bromide.

8. The process of claims 1-7, wherein the reaction is in the presence of a base.

9. The process of claims 1-8, wherein the reaction is in the presence of a base selected from the group consisting of potassium hydroxide, sodium hydroxide, and potassium carbonate.

10. The process of claims 1-9, wherein the reaction is in the presence of potassium carbonate.

11. The process of claims 1-10, wherein the reaction is in the presence of both a base and a catalys

12. The process of claims 1-11, wherein the reaction is in the presence of a base selected from the group consisting of potassium hydroxide, sodium hydroxide, and potassium carbonate, and a catalyst which is a phase transfer catalyst.

13. The process of claims 1-12, wherein the reaction is in the presence of a base selected from the group consisting of potassium hydroxide, sodium hydroxide, and potassium carbonate, and a catalyst selected from the group consisting of tetrabutylammonium bromide and 18-crown-6.

14. The process of claims 1-13, wherein R^1 is at position 6 and R^2 is hydrogen.

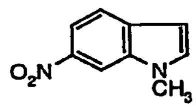
15. The process of claims 1-14, wherein R^1 is nitro.

16. The process of claims 1-13, wherein R^1 is hydrogen and R^2 is acetonitrile.

17. A process for the preparation of 3-(1-methylindol-3-yl)-4-(1-methyl-6-nitroindol-3-yl)-14-pyrrole-2.5-dione comprising

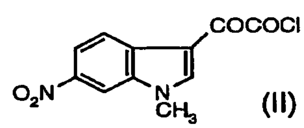
d) a reaction as defined in claims 1 to 16 wherein R^1 is at position 6 and R^2 is hydrogen; followed by

e) a reaction of the compound of formula I



(I)

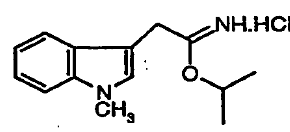
with $(COCI)_2$ to obtain a compound of formula II;



(II)

and

f) coupling a compound of formula II with a compound of formula III



(III)

18. Use of a process of claims 1 to 16 for the preparation of compounds of formula I.

19. Use of a process of claims 1 to 17 for the preparation of 3-(1-methylindol-3-yl)-4-(1-methyl-6-nitroindol-3-yl)-14-pyrrole-2.5-dione.

20. Compounds of formula I prepared by a process of claims 1 to 16.

21. The novel processes and uses described as hereinbefore.

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